Chapter 13
The Impact of Endocrine Disruptors on Female Pubertal Timing*

Jean-Pierre Bourguignon and Anne-Simone Parent

Abstract Secular changes in pubertal timing and particular forms of sexual precocity after migration to new geographical areas whose levels of environment differ from those in the natal country suggest that endocrine-disrupting compounds (EDCs) may be involved. Studies in humans based on measurement of some EDC in relation to pubertal timing are inconclusive for several possible reasons including predominant genetic determinism and effects of complex EDC mixtures. Based on animal models, some possible neuroendocrine mechanisms are discussed as well as the interrelation between the homeostasis of reproduction and energy balance.

Keywords Adiponectin • DDE • Development • DDT • Energy balance • GnRH • Homeostasis • Intrauterine growth retardation • Leptin • Menarche • Nutrition • Puberty • Reproduction

Pubertal Timing as an Endpoint for Endocrine Disruption

Female puberty is the life period when pituitary–ovarian maturation leads to a series of physical changes: initially, onset of breast development and increased height and weight gain; ultimately, first menses (menarche) followed, after months or years, by regular (ovulatory) cycling. A central event in the onset of puberty is an increase in

*This work was supported by grants from the European Commission (EDEN project, contract QLRT-2001-00269), the Fonds National de la Recherche Scientifique (FRS-FNRS 3.4.573.05 F and 3.4.567.09 F), the Faculty of Medicine at the University of Liège (Léon Frédéricq Foundation), and the Belgian Study Group for Paediatric Endocrinology.

J.-P. Bourguignon (✉) • A.-S. Parent
Developmental Neuroendocrinology Unit, GIGA Neurosciences,
University of Liège, Liège, Belgium

Department of Pediatrics, CHU ND des Bruyères, Chênée, Belgium
e-mail: jpbourguignon@ulg.ac.be; asparent@ulg.ac.be

E. Diamanti-Kandarakis and A.C. Gore (eds.), *Endocrine Disruptors and Puberty*,
Contemporary Endocrinology, DOI 10.1007/978-1-60761-561-3_13,

frequency and amplitude of gonadotropin-releasing hormone (GnRH) secretion in the hypothalamus. This event is controlled by redundant inhibitory and excitatory mechanisms that are respectively inactivated and activated at the onset of puberty [1]. For initial pubertal signs (breast development) or subsequent events (menarche), it is generally agreed that timing can vary physiologically within a 5-year period. These variations are predominantly determined by genetic factors, while environmental factors play a comparatively minor role [2]. A striking reflection of environmental effects on pubertal timing arose through the secular advance in menarcheal age. Since this was observed between the mid-nineteenth and the mid-twentieth centuries both in USA and Western Europe and more recently in developing countries [2], improvements in health and nutritional status with industrialization were thought to be an explanation. The end or slowdown of this process between 1960 and 2000 [2] was consistent with that explanation. Two large American studies published around the year 2000 [3, 4] and, very recently, findings obtained in Denmark and Belgium [5, 6] provided evidence of earlier onset of puberty. However, onset of breast development, an initial sign, was more affected than age at menarche, a relatively final pubertal sign [3–6]. Moreover, the age distribution of pubertal signs showed recently skewing toward earlier ages for initial signs [6, 7] and toward later ages for final signs [6]. The latter finding is consistent with a French study showing that the secular trend toward earlier menarcheal age was associated with a trend toward later occurrence of regular (ovulatory) cycling [8]. Because those changes in pubertal timing were concomitant with the epidemic of obesity in USA, the pathophysiological involvement of fat mass, possibly through leptin [3, 4, 9], was hypothesized in that country. However, the early breast development reported recently in Denmark was not significantly associated with changes in adiposity [5]. Thus, the possible involvement of other factors such as endocrine-disrupting chemicals (EDCs) was postulated to account for the current secular changes in pubertal timing [10], though no direct evidence substantiates that hypothesis so far.

Suggestive evidence of environmental effects on female pubertal timing also came from studies in children migrating for international adoption. As cohorts, they appeared to mature earlier than children in the foster countries and in the countries of origin [2, 11]. Also, sexual precocity requiring treatment was seen in those migrating children much more frequently than in others [12, 13]. Increased serum levels of DDE, a persisting derivative of the estrogenic insecticide DDT, were found among migrating children. We therefore hypothesized that early exposure to this EDC and subsequent withdrawal due to migration could account for a neuroendocrine mechanism of secondary central precocious puberty in those girls [2, 12]. Using an immature female rat model exposed during early postnatal life to DDT for 5 days, we have been able to induce sexual precocity with involvement of hypothalamic mechanisms [14, 15]. The involvement of DDT in the pathogenesis of sexual precocity in migrating girls could be further substantiated by the observation of lower serum DDE or DDT levels in the girls with normal or late pubertal timing than in precocious girls. Direct evidence, however, is lacking and difficult to obtain since those girls have no reason to attend the clinic and have a blood sample drawn. Moreover, many other EDCs could have affected the migrating children in early

life, whereas they cannot be identified several years later. Other factors including recovery from earlier nutritional as well as psychosocial deprivation could play some role as well [16]. One further example suggesting EDC-related development of sexual precocity inferred from geographical clusters of children has been reported in Italy, where the mycotoxin zearalenone has been incriminated in increased frequency of sexual precocity [17].

Association Between Exposure to Endocrine Disruptors and Variations in Human Female Pubertal Timing

Linking exposure to particular EDCs and physiological or abnormal variations in pubertal timing is a challenge for several reasons [18, 19]. Humans as well as animals are likely exposed simultaneously to a variety of EDCs acting as mixtures that change in composition and dose with time. Since compounds mixed at concentrations that are inactive when used as single EDCs have been shown to become active when used as mixtures [20], the significance of studies on single-EDC effects is limited, and addition of the effects of several individual EDCs cannot predict the effect of mixtures. The study of mixtures, however, is complex and laborious. So far, studies on EDC effects on pubertal timing have been performed with single classes of EDCs only. When exposure is assessed at the time of pubertal development or disorders, the identified EDCs could be different from those which were acting during fetal/perinatal life, a most critical time for EDC effects on pubertal timing [20, 21]. Keeping in mind that the relevance of the studied relationship between EDCs and pubertal disorders is limited due to the above reasons; the available information mainly based on the study of single EDCs is summarized in Tables 13.1 (breast development) and 13.2 (menarche). Prenatal and postnatal exposures are separated whenever possible.

Links between EDCs and puberty have been evaluated in some experimental studies. After exposure to the insecticide DDT or its derivative DDE, discrepant data were obtained since early onset of breast development [12] and early menarche [22, 23] were observed in some studies, whereas others found female pubertal timing to be within normal age limits [24–26]. In the female monkey, delayed nipple growth and short follicular phase were seen after exposure to the pesticide methoxychlor [27]. The timing of breast development was not affected after exposure to polybrominated biphenyls (PBBs) or polychlorinated biphenyls (PCBs) [24, 26, 28, 29]. Early menarche, however, was reported after exposure to PBBs [28] or PCBs [25], though several studies found no alteration of menarcheal age in association with PCBs [22, 24, 29, 30]. Dioxins differentially affected timing of breast development that was delayed [29, 31] and timing of menarche that was normal [29, 31, 32]. Early breast development was reported in association with postnatal exposure to phthalates [33, 34]. Phytoestrogens were associated with delayed timing of breast development [26, 34] but no effects on menarcheal age [35]. The discrepant findings for breast development and menarche emphasize the importance of studying

Table 13.1 Variations in timing of onset of breast development in relation to pre- and/or postnatal exposure to endocrine disrupters

Pubertal timing	Early			Normal			Delayed		
Exposure	Prenatal	Postnatal	Unspecified	Prenatal	Postnatal	Unspecified	Prenatal	Postnatal	Unspecified
DDE (+ DDT)			Krstevska-Konstantinova et al., [12]		Wolff et al., [25]	Gladen et al., [23]			
Methoxychlor									
PBBs						Blanck et al., [27]			
PCBs					Den Hond et al., [28]; Wolff etal., [25]				
						Gladen et al., [23]			
Dioxins							Leijs et al., [30]	Den Hond et al., [28]	
Phthalates		Colon et al., [32]; Wolff et al., [33]							
Phytoestrogens soy formula								Wolff et al., [25, 33]	

DDE dichlorodiphenylchloroethane, *DDT* dichlorodiphenyltrichloroethane, *PBB* polybrominated biphenyl, *PCB* polychlorinated biphenyl, *B*2, *B*3 Tanner's stages 2 and 3 of breast development (Modified from Ref. [19])

Table 13.2 Variations in timing of menarche in relation with pre- and/or postnatal exposure to endocrine disrupters

Pubertal timing	Early			Normal			Delayed		
Exposure	Prenatal	Postnatal	Unspecified	Prenatal	Postnatal	Unspecified	Prenatal	Postnatal	Unspecified
DDE (+ DDT)	Vasiliu et al., [21]	Ouyang et al., [22]			Denham et al., [24]	Gladen et al., [23]			
Methoxychlor								(Monkey) Golub et al., [26]	
PBBs			Blanck et al., [27]						
PCBs		Denham et al., [24]		Vasiliu et al., [29]; Yang et al., [30]	Den Hond et al., [28]	Gladen et al., [23]			
Dioxins				Leijs et al., [30] Warner et al., [31]	Den Hond et al., [28]				
Phthalates									
Phytoestrogens soy formula					Strom et al., [34]				

DDE dichlorodiphenylchloroethane, *DDT* dichlorodiphenyltrichloroethane, *PBB* polybrominated biphenyl, *PCB* polychlorinated biphenyl, *B*2, *B*3 Tanner's stages 2 and 3 of breast development (modified from Ref. [19])

different pubertal signs, possibly involving different mechanisms at several times throughout the pubertal process. Overall, those studies did not enable a differentiation of effects depending on prenatal or postnatal period of exposure to the EDCs.

Possible Mechanisms of EDC Effects on Female Sexual Maturation

Overall, most EDC interactions with sex steroid effects are translated into either estrogen agonist action or androgen antagonism with the ratio of estrogen/androgen actions as an ultimate determinant [36]. In concordance with this concept, premature breast development can occur after exposure to phthalates that are considered to act primarily as androgen antagonists [33]. Because sex steroids can act at the different levels of the hypothalamic–pituitary–gonadal system (Table 13.3), the imbalance between estrogen and androgen effects caused by EDCs potentially affects all those levels. Direct disruption of the peripheral female reproductive system involves predominantly effects mimicking estrogens [19]. Such direct peripheral effects of EDCs could influence the circulating levels of endogenous peripheral hormones. Then, changes in neuroendocrine and pituitary function could result indirectly from altered peripheral feedback. Alternatively or additionally, changes in hypothalamic and pituitary function could result directly from EDC neuroendocrine effects as illustrated by alteration of the preovulatory gonadotropin surge following exposure to sex steroids during fetal or perinatal life [37]. Female pubertal development can involve either hypothalamic–

Table 13.3 Some possible mechanisms of EDC maturational effects on the hypothalamic–pituitary–gonadal system in female individuals

Level possibly targeted by EDCs	Developmental effects of increased estrogen/androgen balance	Mechanisms
Central nervous system: suprahypothalamic afferents	Structural changes?	Primary central/ neuroendocrine or secondary to altered feedback effects of gonadal hormones
Hypothalamus: GnRH neurons and surrounding neuronal–glial system	Facilitation (or inhibition) of pulsatile GnRH secretion Female more sensitive than the male? Alteration of sexually dimorphic control of ovulation	
Pituitary gland: gonadotrophic cells	Early pubertal stimulation or increased prepubertal inhibition (negative feedback)	Response to neuroendocrine effects or peripheral feedback
Gonads: sex steroid production/ effects and gametogenesis	Alteration of folliculogenesis	Primary peripheral or secondary to altered neuroendocrine control
Peripheral tissues: Sex steroid effects	Early/increased stimulation of estrogen-sensitive tissues (breast, uterus)	

pituitary maturation that will secondarily increase sex steroid secretion or direct peripheral interaction in the tissues targeted by sex steroids or both mechanisms.

Due to obvious limits in assessment of neuroendocrine function in the clinical setting, the use of experimental models is required to tackle neuroendocrine effects of EDCs. We exposed female rats early and transiently to DDT in order to mimic the conditions thought to account for sexual precocity in girls migrating for international adoption [2, 12]. Because fetal or early postnatal exposure to testosterone or estradiol would masculinize the CNS and alter the neuroendocrine mechanism of estradiol stimulation of GnRH secretion [38], the animals were exposed to DDT starting postnatal day 6 until day 10. Ex vivo study of GnRH release from hypothalamic explants showed premature acceleration of pulsatile GnRH secretion, early vaginal opening, and early first estrus [14]. Further evidence of possible hypothalamic–pituitary effects of DDT in vivo was obtained through a premature developmental reduction in LH response [14]. Our interpretation of sexual precocity after migration [2, 14] is that during exposure to DDT, estrogenic effects can account for both peripheral and central (neuroendocrine) stimulation. However, due to concomitant negative feedback inhibition at the pituitary level, the central effects are not translated into gonadotropin stimulation of the ovaries until the pituitary inhibition disappears following migration in a DDT-free environment. In a study of internationally adopted girls aged 5–8 years, Teilmann and coworkers [39] reported that serum FSH and estradiol levels were already elevated in several girls before they eventually showed clinical evidence of sexual precocity, confirming early pituitary–ovarian activity after migration. The above mechanism is comparable to that operating in other conditions with peripheral precocious puberty (e.g., congenital adrenal hyperplasia, adrenal or gonadal tumors) followed by secondary central precocious puberty after the peripheral disorder is cured by medical or surgical treatment [2]. Consistent with this concept, central precocity should not be manifested in conditions of persisting exposure to DDT. We attempted to demonstrate that continued administration of DDT to the female rats was not associated with evidence of precocious central maturation, but we failed due to toxic effects including malnourishment and growth failure [14].

The effects of EDCs on sexual maturation in laboratory rodents were reviewed previously [40]. Using triphenyltin in the female rat [41] and phthalates in the male [42], peripheral effects can be biphasic, low or high doses causing early or delayed puberty, respectively. In the few studies where hypothalamic–pituitary function was assessed, LH secretion was reduced together with early vaginal opening after DES [43] or irregular cycling after BPA [44]. Still, the possibly coexisting central and peripheral effects remain a matter of confusion, and the early developmental reduction in LH secretory response to GnRH in the rat [14] is difficult to separate from negative feedback inhibition. As another example, BPA administration to neonatal female rats for 4 days resulted in early vaginal opening and acyclicity but no change in sexual receptivity and FOS induction in GnRH neurons after steroid priming [45]. This suggests predominant peripheral effects in those conditions and highlights the importance of simultaneous study of central and peripheral effects.

Further elucidation of EDC involvement in the neuroendocrine mechanism of female sexual precocity may come from recent progress in identification of estrogen-responsive cells – neurons and/or glial cells through expression of ER alpha and/or ER beta and nongenomic effects and estrogen-responsive genes. Based on murine and ovine animal studies on the sex steroid feedback control of the ovulatory cycle, it appears that GnRH neurons are unlikely to respond directly to stimulatory effects of estrogens that are mediated through afferent neurons [46–48]. Among them, the kisspeptin neurons appear to play an important role as estrogen-sensitive final gate to the GnRH neurons [48, 49] with a gender dimorphism that could account for the female predominance of sexual precocity. This mechanistic hypothesis is consistent with preliminary data showing higher peripheral kisspeptin levels in patients with precocious puberty than in controls [50]. Not only estrogens or estrogenic compounds of peripheral or environmental origin could influence that system but also locally originating estrogens through brain aromatase [51]. Nongenomic interactions of estrogens with the GnRH neurons were reported besides the effects mediated through kisspeptin neurons in the monkey [52]. Recent studies indicate that kisspeptin expression or kisspeptin fiber density in the rodent hypothalamus is reduced after neonatal exposure to BPA [53] or genistein [54], respectively. Though these data suggest negative feedback effects of those EDCs, further studies with emphasis on developmental changes are needed to substantiate or invalidate the involvement of kisspeptin in possible stimulatory effects of EDCs on pubertal timing.

Female Sexual Precocity: An Early Homeostatic Disturbance Involving the Control of Reproduction and Energy Balance?

The hypothalamic–neuroendocrine system is a common integrative site for regulation of homeostasis including reproduction and energy balance. That regulation likely involves, during fetal and neonatal life, programming mechanisms that account for the "developmental origin of health and diseases" [55]. Peripheral messengers from the gonads (e.g., sex steroids) and from adipose tissue (e.g., leptin, adiponectin) can also play important regulatory roles in linking energy balance and reproduction throughout life. In Table 13.4 are proposed some of the connections between homeostasis of reproduction and homeostasis of energy balance, throughout life, as discussed in two recent reviews [20, 21]. Feto-maternal malnourishment or overfeeding with fat as well as fetal exposure to sex steroids or EDCs such as DES and BPA were shown to possibly result in low birth weight, early puberty, ovulatory disorders, obesity in adulthood, and metabolic syndrome [55–58]. Some of those effects are sexually dimorphic since DES causes a metabolic syndrome in female but not in male mice [56]. Both sex steroids and leptin are involved in early organizational effects in the hypothalamus that could affect, respectively, the central control of reproduction [59] and energy balance [60]. There are several lines of experimental and clinical evidence of cross talk between the systems controlling reproduction and

Table 13.4 Some characteristics shared in disorders of homeostasis of reproduction and energy balance

Environmental stressors in fetal life	Endocrine-disrupting chemicals (EDCs)	Under- / Over-feeding	Examples of interaction
Neuroendocrine endpoint	Estrogen/androgen balance	Energy balance	DES-induced late obesity and metabolic syndrome
Ante-/neonatal programming	Estrogen-mediated brain masculinization	Leptin-mediated brain organization	Leptin permissive for puberty and reproduction
Neonatal manifestations	Disorders of sex differentiation	Low birth weight	Combined anomalies
Late manifestations	Disorders of puberty and reproduction	Obesity and metabolic syndrome	Combined anomalies

energy balance. During postnatal life, leptin is an important link between energy balance and reproduction through facilitatory effects on GnRH secretion [2, 61]. Clinically, cross talk is supported by the recent finding that rapid weight gain in infancy between birth and 9 months predicts increased adiposity at 10 years and early menarcheal age [62]. Ibanez et al. [63] reported that intrauterine growth retardation (IUGR) was associated with increased risk of premature pubarche, hyperinsulinism, ovarian hyperandrogenism, and polycystic ovary syndrome (PCOS). Of particular interest is the observation that IUGR is associated with increased visceral adiposity and reduced serum levels of adiponectin in childhood [64]. The latter effect parallels BPA-induced reduction of adiponectin production by adipocytes [65, 66]. All together, those findings suggest that both the reproductive and energy balance systems share a possible fetal/early postnatal determinism of disorders such as sexual precocity under the influence of early nutritional conditions and/or early exposure to EDCs, with mechanistic cross talk between the two systems.

References

1. Bourguignon JP. Control of the onset of puberty. In: Pescovitz OH, Eugster E, editors. Pediatric endocrinology: mechanisms, manifestations and management. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 285–98.
2. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev. 2003;24:668–93.
3. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings Network. Pediatrics. 1997;99:505–12.
4. Lee PA, Guo SS, Kulin HE. Age of puberty: data from the United States of America. APMIS. 2001;109:81–8.

5. Aksglaede L, Sørensen K, Petersen JH, Skakkebæk NE, Juul A. Recent decline in age at breast development: the Copenhagen Puberty Study. Pediatrics. 2009;123:e932–9.
6. Roelants M, Hauspie R, Hoppenbrouwers K. References for growth and pubertal development from birth to 21 years in Flanders, Belgium. Ann Hum Biol. 2009;36:680–94.
7. Papadimitriou A, Pantsiotou S, Douros K, Papadimitriou DT, Nicolaidou P, Fretzayas A. Timing of pubertal onset in girls: evidence for non-gaussian distribution. J Clin Endocrinol Metab. 2008;93:4422–5.
8. Clavel-Chapelon F. E3N-EPIC (European prospective investigation into cancer) Group Evolution of age at menarche and at onset of regular cycling in a large cohort of French women. Hum Reprod. 2002;17:228–32.
9. Himes JH. Examining the evidence for recent secular changes in the timing of puberty in US children in light of increases in the prevalence of obesity. Mol Cell Endocrinol. 2006;254–255: 13–21.
10. Teilmann G, Juul A, Skakkebaek NE, Toppari J. Putative effects of endocrine disrupters on pubertal development in the human. Best Pract Res Clin Endocrinol Metab. 2002;16:105–21.
11. Proos LA, Hofvander Y, Tuvemo T. Menarcheal age and growth pattern of Indian girls adopted in Sweden. I. Menarcheal age. Acta Paediatr Scand. 1991;80:852–8.
12. Krstevska-Konstantinova M, Charlier C, Craen M, Du Caju M, Heinrichs C, de Beaufort C, Plomteux G, Bourguignon JP. Sexual precocity after immigration from developing countries to Belgium: evidence of previous exposure to organochlorine pesticides. Hum Reprod. 2001;16:1020–6.
13. Teilmann G, Pedersen CB, Skakkebæk NE, Jensen TK. Increased risk of precocious puberty in internationally adopted children in Denmark. Pediatrics. 2006;118:e391–9.
14. Rasier G, Parent AS, Gérard A, Lebrethon MC, Bourguignon JP. Early maturation of gonadotropin-releasing hormone secretion and sexual precocity after exposure of infantile female rats to estradiol or dichlorodiphenyltrichloroethane. Biol Reprod. 2007;77:734–42.
15. Rasier G, Parent AS, Gérard A, Denooz R, Lebrethon MC, Charlier C, Bourguignon JP. Mechanisms of interaction of endocrine disrupting chemicals with glutamate-evoked secretion of gonadotropin-releasing hormone. Toxicol Sci. 2008;102:33–41.
16. Dominé F, Parent AS, Rasier G, Lebrethon MC, Bourguignon JP. Assessment and mechanism of variations in pubertal timing in internationally adopted children: a developmental hypothesis. Eur J Endocrinol. 2006;155:S17–25.
17. Massart F, Saggese G. Oestrogenic mycotoxin exposures and precocious pubertal development. Int J Androl. 2010;33:369–76.
18. Buck Louis GM, Gray Jr LE, Michele Marcus M, Ojeda S, Pescovitz OA, Feldman Witchel S, Sippell W, Abbott DA, Soto A, Tyl RW, Bourguignon JP, Skakkebaek NE, Swan SH, Golub MS, Wabitsch M, Toppari J, Euling SY. Environmental factors and puberty timing: expert panel research needs. Pediatrics. 2008;121(suppl3):S192–207.
19. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev. 2009;30:293–342.
20. Bourguignon JP, Rasier G, Lebrethon MC, Gérard A, Naveau E, Parent AS. Neuroendocrine disruption of pubertal timing and interactions between homeostasis of reproduction and energy balance. Mol Cell Endocrinol. 2010;324:110–20.
21. Bourguignon JP, Parent AS. Early homeostatic disturbances of human growth and maturation by endocrine disrupters. Curr Opin Pediatr. 2010;22:470–7.
22. Vasiliu O, Muttineni J, Karmaus W. In utero exposure to organochlorines and age at menarche. Hum Reprod. 2004;19:1506–12.
23. Ouyang F, Perry MJ, Venners SA, Chen C, Wang B, Yang G, Fang Z, Zang T, Wang L, Xu X, Wang X. Serum DDT, age at menarche, and abnormal menstrual cycle length. Occup Environ Med. 2005;62:878–84.
24. Gladen BC, Ragan B, Rogan WJ. Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene. J Pediatr. 2000;136:490–6.

25. Denham M, Schell LM, Deane G, et al. Relationship of lead, mercury, mirex, dichlorodiphenyldichloroethylene, hexachlorobenzene, and polychlorinated biphenyls to timing of menarche among Akwesasne Mohawk girls. Pediatrics. 2005;115:e127–34.
26. Wolff MS, Britton JA, Boguski L, et al. Environmental exposures and puberty in inner-city girls. Environ Res. 2008;107:393–400.
27. Golub MS, Hogrefe CE, Germann SL, Lasley BL, Natarajan K, Tarantal AF. Effects of exogenous estrogenic agents on pubertal growth and reproductive system maturation in female Rhesus monkeys. Toxicol Sci. 2003;74:103–13.
28. Blanck HM, Marcus M, Tolbert PE, et al. Age at menarche and tanner stage in girls exposed in utero and postnatally to polybrominated biphenyl. Epidemiology. 2000;11:641–7.
29. Den Hond E, Roels HA, Hoppenbrouwers K, et al. Sexual maturation in relation to polychlorinated aromatic hydrocarbons: Sharpe and Skakkebaek's hypothesis revisited. Environ Health Perspect. 2002;110:771–6.
30. Yang CY, Yu ML, Guo HR, Lai TJ, Hsu CC, Lambert G, Guo YL. The endocrine and reproductive function of the female Yucheng adolescents prenatally exposed to PCBs/PCDFs. Chemosphere. 2005;61:355–60.
31. Leijs MM, Koppe JG, Olie K, et al. Delayed initiation of breast development in girls with higher prenatal dioxin exposure; a longitudinal cohort study. Chemosphere. 2008;73:999–1004.
32. Warner M, Samuels S, Mocarelli P, et al. Serum dioxin concentrations and age at menarche. Environ Health Perspect. 2004;112:1289–92.
33. Colon I, Caro D, Bourdony CJ, Rosario O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. Environ Health Perspect. 2000;108:895–900.
34. Wolff MS, Teitelbaum SL, Pinney SM, Windham G, Liao L, Biro F, Kushi LH, Erdmann C, Hiatt RA, Rybak ME, Calafat AML and the Breast Cancer and Environment Research Centers. Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls. Environ Health Perspect. 2010;118:1039–46.
35. Strom BL, Schinnar R, Ekhard E, Ziegler EE, Kurt T, Barnhart MD, Mary D, Sammel ScD, George A, Macones MD, Virginia A, Stallings MD, Jean M, Drulis BA, Steven E, Nelson BA, Sandra A, Hanson BA. Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. JAMA. 2001;286:807–14.
36. Rivas A, Fisher J, McKinnell C, Atanassova N, Sharpe RM. Induction of reproductive tract developmental abnormalities in the male rat by lowering androgen production or action in combination with a low dose of diethylstilbestrol: evidence for importance of the androgen-estrogen balance. Endocrinology. 2002;143:4797–808.
37. Gorski RA. Influence of age on a perinatal administration of a low dose of androgen. Endocrinology. 1968;82:1001–4.
38. Matagne V, Rasier G, Lebrethon MC, Gérard A, Bourguignon JP. Estradiol stimulation of pulsatile GnRH secretion in vitro: correlation with perinatal exposure to sex steroids and induction of sexual precocity in vivo. Endocrinology. 2004;145:2775–83.
39. Teilmann G, Boas M, Petersen JH, Main KM, Gormsen M, Damgaard K, Brocks V, Skakkebæk NE, Jensen KT. Early pituitary-gonadal activation in 5–8 years old adopted girls before clinical signs of puberty: a study of 99 foreign adopted girls and 93 controls. J Clin Endocrinol Metab. 2007;92:2538–44.
40. Rasier G, Toppari J, Parent AS, Bourguignon JP. Female sexual maturation and reproduction after prepubertal exposure to estrogens and endocrine disrupting chemicals: a review of rodent and human data. Mol Cell Endocrinol. 2006;254–255:187–201.
41. Grote K, Andrade AJM, Wichert Grande S, Kuriyama SN, Talsness CE, Appel KE, Chahouda I. Effects of peripubertal exposure to triphenyltin on female sexual development of the rat. Toxicology. 2006;222:17–24.
42. Ge RS, Chen GR, Dong Q, Akingbemi B, Sottas CM, Santos M, Sealfon SC, Bernard DJ, Hardy MP. Biphasic effects of postnatal exposure to diethylhexylphthalate on the timing of puberty in male rats. J Androl. 2007;28:513–20.

43. Kubo K, Arai O, Omura M, Watanabe R, Ogata R, Aou S. Low-dose effects of bisphenol A on sexual differentiation of the brain and behavior in rats. Neurosci Res. 2003;45:345–56.
44. Rubin BL, Murray MK, Damassa DA, King JC, Soto AM. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity and plasma LH levels. Environ Health Perspect. 2001;109:675–80.
45. Adewale HB, Jefferson WN, Newbold RR, Patisaul HB. Neonatal bisphenol-A exposure alters rat reproductive development and ovarian morphology without impairing activation of gonadotropin-releasing hormone neurons. Biol Reprod. 2009;81:690–9.
46. Herbison AE. Estrogen positive feedback to gonadotropin-releasing hormone (GnRH) neurons in the rodent: the case for the rostral periventricular area of the third ventricle (RP3V). Brain Res Rev. 2008;57:277–87.
47. Goodman RL, Jansen HT, Billings HJ, Coolen LM, Lehman MN. Neural systems mediating seasonal breeding in the ewe. J Neuroendocrinol. 2010;22:674–81.
48. Caraty A, Franceschini I, Hoffman GE. Kisspeptin and the preovulatory gonadotrophin-releasing hormone/luteinising hormone surge in the ewe: Basic aspects and potential applications in the control of ovulation. J Neuroendocrinol. 2010;22:710–5.
49. Kauffman AS. Gonadal and nongonadal regulation of sex differences in hypothalamic Kiss1 neurones. J Neuroendocrinol. 2010;22:682–91.
50. de Vries L, Shtaif B, Phillip M, Gat-Yablonski G. Kisspeptin serum levels in girls with central precocious puberty. Clin Endocrinol. 2009;71:524–8.
51. Cornil CA, Charlier TD. Rapid behavioural effects of oestrogens and fast regulation of their local synthesis by brain aromatase. J Neuroendocrinol. 2010;22:664–73.
52. Terasawa E, Kurian JR, Guerriero KA, Kenealy BP, Hutz ED, Keen KL. Recent discoveries on the control of gonadotrophin-releasing hormone neurones in nonhuman primates. J Neuroendocrinol. 2010;22:630–8.
53. Navarro VM, Sanchez-Garrido MA, Castellano JM, Roa J, García-Galiano D, Pineda R, Aguilar E, Pinilla L, Tena-Sempere M. Persistent impairment of hypothalamic KiSS-1 system after exposures to estrogenic compounds at critical periods of brain sex differentiation. Endocrinology. 2009;150:2359–67.
54. Bateman HL, Patisaul HB. Disrupted female reproductive physiology following neonatal exposure to phytoestrogens or estrogen specific ligands is associated with decreased GnRH activation and kisspeptin fiber density in the hypothalamus. Neurotoxicology. 2008;29:988–97.
55. Gluckman PD, Hanson MA. The developmental origins of the metabolic syndrome. Trends Endocrinol Metab. 2004;15:183–7.
56. Newbold RR, Padilla-Banks E, Jefferson WN. Environmental estrogens and obesity. Mol Cell Endocrinol. 2009;304:84–9.
57. Sloboda DM, Howie GJ, Pleasants A, Gluckman PD, Vickers MH. Pre- and postnatal nutritional histories influence reproductive maturation and ovarian function in the rat. PLoS One. 2009;4:e6744.
58. Heindel JJ, vom Saal FS. Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity. Mol Cell Endocrinol. 2009;304:90–6.
59. McCarthy MM, Auger AP, Bale TL, De Vries GJ, Dunn GA, Forger NG, Murray EK, Nugent BM, Schwarz JM, Wilson ME. The epigenetics of sex differences in the brain. J Neurosci. 2009;29:12815–23.
60. Bouret SG. Role of early hormonal and nutritional experiences in shaping feeding behavior and hypothalamic development. J Nutr. 2010;140:653–7.
61. Lebrethon MC, Aganina A, Fournier M, Gérard A, Parent AS, Bourguignon JP. Effects of in vivo and in vitro administration of ghrelin, leptin and neuropeptide mediators on pulsatile gonadotrophin-releasing hormone secretion from male rat hypothalamus before and after puberty. J Neuroendocrinol. 2007;19:181–8.
62. Ong KK, Emmett P, Northstone K, Golding J, Rogers I, Ness AR, Wells JC, Dunger DB. Infancy weight gain predicts childhood body fat and age at menarche in girls. J Clin Endocrinol Metab. 2009;94:1527–32.

63. Ibáñez L, Francois I, Potau N, de Zegher F. Precocious pubarche, hyperinsulinism and ovarian hyperandrogenism in girls: relation to reduced fetal growth. J Clin Endocrinol Metab. 1998;83: 3558–662.
64. Ibáñez L, Lopez-Bermejo A, Díaz M, Suarez L, de Zegher F. Low-birth weight children develop lower sex hormone binding globulin and higher dehydroepiandrosterone sulfate levels and aggravate their visceral adiposity and hypoadiponectinemia between six and eight years of age. J Clin Endocrinol Metab. 2009;94:3696–9.
65. Somm E, Schwitzgebel VM, Toulotte A, Cederroth CR, Combescure C, Nef S, Aubert ML, Hüppi PS. Perinatal exposure to bisphenol A alters early adipogenesis in the rat. Environ Health Perspect. 2009;117:1549–55.
66. Hugo ER, Brandebourg TD, Woo JG, Loftus J, Alexander JW, Ben-Jonathan N. Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes. Environ Health Perspect. 2008;116:1642–7.